Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-45 and 48-65 are pending in the application, with claim 1 being the sole independent claim. Claims 69-80 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claims 37, 45 and 48-52, and 58 are withdrawn from consideration by the Examiner as being drawn to non-elected inventions or non-elected species, but remain pending. Based on the following remarks, as well as the remarks set forth in Applicants' reply of August 23, 2006 (incorporated herein by reference in its entirety), Applicants respectfully request that the Examiner reconsider all outstanding rejections and that they be withdrawn.

I. Claim Rejections Under 35 U.S.C. § 103

A. Marasco In View of Waterhouse

Claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71 and 75-79 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Marasco *et al.*, U.S. Patent No. 5,851,829 ("Marasco") in view of Waterhouse *et al.*, *Nucl. Acids Res. 21*:2265-2266 (1993) ("Waterhouse"), as evidenced by International Committee on Taxonomy of Viruses and Wikipedia, the Free Encyclopedia. (Office Action, page 3). Applicants respectfully traverse this rejection.

A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re*

Rijckaert, 9 F.3d 1531, 1533 (Fed. Cir. 1993). "[I]t is insufficient to merely identify each element in the prior art to establish unpatentability of the combined subject matter as a whole." *Sanofi-Synthelabo v. Apotex*, 470 F.3d 1368, 1370 (Fed. Cir. 2006) (citing Abbott Labs. v. Andrx Pharm., Inc., 452 F.3d 1331, 1336 (Fed Cir. 2006)). Rather, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). A showing of combinability of references, in whatever form, must be "clear and particular." *See In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Dembiczak*, 175 F.3d at 999, 50 USPQ2d at 1617.

As explained below, not all of the elements of the claims are taught or suggested by the cited references. In addition, a person of ordinary skill in the art would not have been motivated to combine or modify the teachings of the cited references. Therefore, a *prima facie* case of obviousness has not been established.

1. Not All Elements of the Claims Are Taught or Suggested by the Cited References

Independent claim 1 is directed, in general terms, to a screening method that identifies polynucleotides encoding an intracellular immunoglobulin molecule or a fragment thereof. Expression of the immunoglobulin induces a modified phenotype in a eukaryotic host cell by binding to an intracellular antigen.

The method of claim 1 comprises, *inter alia*, the intracellular combination of (1) an immunoglobulin subunit polypeptide comprising a heavy chain (or light chain) variable region, and (2) an immunoglobulin subunit polypeptide comprising a light chain (or heavy chain) variable region, to form (3) an intracellular immunoglobulin molecule (or fragment thereof). If the intracellular immunoglobulin molecule is able to bind to an intracellular antigen and thereby induce a modified phenotype, the cells are identified and the polynucleotides from the first library are recovered. By this method, one can identify from a library of polynucleotide molecules those that encode an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region that is capable of binding to a specific antigen. This process represents a unique screening method that is neither taught nor suggested by the cited references.

(a) The Cited References Do Not Teach or Suggest an Intracellular Screening Method of the Present Claims

Applicants respectfully maintain that the cited references do not teach or suggest a method of selecting polynucleotides that encode an intracellular immunoglobulin molecule or fragment thereof, whose expression induces a modified phenotype in a eukaryotic host cell upon binding to an intracellular antigen. The Examiner, in maintaining the obviousness rejection, again asserts that

> [i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made *to screen a library of intracellular antibodies as taught by Marasco et al.* using two libraries (i.e., a library of heavy and light chains) as taught by Waterhouse et al. because Waterhouse explicitly state that both the heavy and light chain regions can be varied simultaneously (e.g., see Waterhouse, column 1).

Office Action at page 10 (emphasis added). However, as set forth in Applicants' reply filed on August 23, 2006 (incorporated herein by reference in its entirety), Marasco does not teach screening a library of intracellular antibodies.

To further address this issue, Applicants submit herewith as Exhibit A the Declaration under 37 C.F.R. § 1.132 of Dr. Maurice Zauderer, an expert in immunology and a co-inventor of the captioned application. As explained by Dr. Zauderer, Marasco's method first identifies an antibody of interest by traditional extracellular screening methods, *then* expresses the individual, pre-selected antibody intracellularly as a fragment. Exhibit A at page 3. This process is completely different than the method of the claimed invention. Furthermore, as stated by Dr. Zauderer, the only specific screening methods disclosed in Marasco, *i.e.*, phage display, passing cell culture supernatants over affinity columns, mini-gel filtration, radioimmunoassay with magnetic beads, biosensor-based analysis (*e.g.*, BIAcore), and ELISA, are all extracellular identification methods. Exhibit A at page 4. None of these screening techniques is performed using libraries of intracellular immunoglobulins that bind an intracellular antigen. Marasco does not even suggest that it is possible to screen libraries of intracellularly expressed immunoglobulins, let alone teach one of ordinary skill in the art how it would be accomplished. Therefore, Marasco, the primary reference cited by the Examiner in the obviousness rejection, does not teach the elements of the claimed invention for which the Examiner relies on it.

Moreover, Waterhouse, the secondary reference cited by the Examiner, discloses only phage display methods. Screening of immunoglobulin phage display libraries is performed extracellularly, *e.g.*, by panning phage on antigen coated plates or by collecting

culture supernatant containing phage particles that have been secreted from the bacterial host cells. *See, e.g.,* Roitt *et al.* IMMUNOLOGY (6th ed., 2001) at page 426 (attached hereto as Exhibit B); *see also* Waterhouse at page 2266, figure 1 legend ("About 10^{10} tu phage fd particles (including recombinant phage) were harvested *from the culture supernatant* by centrifuging out bacteria at 130000 g for 5 min. and passing the supernatant through a 0.45 μm filter []."") (emphasis added). Hence, Waterhouse does not cure the deficiencies of Marasco because Waterhouse does not describe expression of even a single intracellular immunoglobulin, let alone a method of selecting polynucleotides from intracellularly expressed *libraries* of immunoglobulins as in the present invention. Thus, even in combination, these references do not teach all of the elements of the claimed invention, and a *prima facie* case of obviousness has not been established.

2. A Person of Ordinary Skill in the Art Would Not Have Been Motivated to Modify or Combine the Cited References

Not only does the combination of Marasco and Waterhouse fail to teach or suggest all of the elements of the present invention, one of ordinary skill in the art would not have been motivated to modify or combine these references. As set forth in Applicants' reply of August 23, 2006, a person of ordinary skill in the art would have had absolutely no motivation to modify the screening method of Marasco by introducing a *second* library of polynucleotides into the cells, as specified by the present claims. The F105 single chain antibody of Marasco contains *both* a heavy chain variable region *and* a light chain variable region. *See* Marasco, Fig. 2. Thus, the F105 single chain antibody -- by itself -- is capable of binding to the gp120 antigen. Accordingly, a person of ordinary skill in the art would have had no reason to introduce even a *single* second polynucleotide encoding a second

immunoglobulin subunit polypeptide into the cells used in Marasco, much less a *library* of polynucleotides encoding a plurality of intracellular immunoglobulin subunit polypeptides, as required by the present claims.

The Examiner nevertheless maintains that "a person of ordinary skill in the art would have been motivated to use two libraries to increase the affinity of the antibody." Office Action at page 24. According to the Examiner, "Marasco et al state, 'mutants having different binding affinities to the envelope glycoprotein [can be] screened' . . . which demonstrates a need for high affinity antibodies." *Id.* However, the Examiner still has not provided any explanation of how the addition of a second library encoding a plurality of second intracellular immunoglobulin subunit polypeptides could possibly "increase the affinity" of the single chain antibody of Marasco. Indeed, the addition of an immunoglobulin subunit polypeptide comprising a heavy or light chain variable region to a single chain antibody would *not* be expected to increase the affinity of the single chain antibody for its antigen. Furthermore, it is even stated in Marasco that,

> [i]n order to keep these antibodies in the cell, it is preferable that the expressed antibody does not contain the entire constant region domains. ... For example, we have constructed a broadly neutralizing sFv antibody to an envelope glycoprotein that contains only six amino acids of the constant region which is not secreted in any large amount by the cell, *whereas the unaltered Fab antibody to such protein is secreted.*

Marasco at col. 20, ll. 36-44 (emphasis added). Thus, one of skill in the art actually would have been deterred from using an Fab fragment that contains heavy and light chain constant regions as disclosed in Waterhouse for intracellular expression as in Marasco. Accordingly,

a person of ordinary skill in the art would have had no motivation to modify or combine the cited references.

3. Summary

For the reasons set forth above, a person of ordinary skill in the art would not have been motivated to modify or combine the cited references. In addition, not all elements of the currently pending claims are taught or suggested by the cited references. Even if one were somehow motivated to combine Waterhouse and Marasco, the most that would be achieved is a method whereby one uses the extracellular phage display screening method disclosed in Waterhouse to pre-select an Fab fragment of interest, then modifies the individual, pre-selected Fab fragment to express it intracellularly as an sFv. However, a method that falls within the scope of the present claims would not be obtained. In view of the foregoing, Applicants respectfully request that this rejection be reconsidered and withdrawn.

B. Marasco In View of Waterhouse, Rowlands and Zauderer

Claims 1-36, 38-44, 53-57, 59-65 and 69-79 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Marasco in view of Waterhouse and further in view of Rowlands *et al.*, WO 93/01296 ("Rowlands") and Zauderer *et al.*, WO 00/28016, ("Zauderer"), as evidenced by International Committee on Taxonomy of Viruses and Wikipedia, the Free Encyclopedia. (Office Action, pages 11-12). Applicants respectfully traverse this rejection.

This rejection relies on the alleged combination of Marasco and Waterhouse to arrive at the subject matter of claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71 and 75-79.

(*See* Office Action, page 11). Rowlands and Zauderer are cited as allegedly teaching the claim limitations that are absent in Marasco and Waterhouse. (*See* Office Action, pages 11-15). As explained in detail in *Section I.A*, above, the rejection of claims 1, 9-19, 21, 24-32, 38-41, 53-57, 59-62, 69-71 and 75-79 under 35 U.S.C. § 103 based on Marasco and Waterhouse is in error because not all elements of the claims are taught or suggested by these references, and a person of ordinary skill in the art would not have been motivated to modify or combine the references. Neither Rowlands nor Zauderer cure the deficiencies of Marasco and Waterhouse, and neither reference provides a motivation to modify or combine the cited references to arrive at a method that falls within the scope of the currently presented claims. Applicants therefore respectfully request that the rejection of claims 1-36, 38-44, 53-57, 59-65 and 69-79 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

II. Obviousness-Type Double Patenting

A. The '456 Application In View of Marasco, Rowlands and Zauderer

Claims 1-36, 38-44, 53-57, 59-65 and 69-79 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 84-122 of U.S. Patent Application No. 09/987,456 ("the '456 application"), in view of Marasco, Rowlands and Zauderer. (Office Action, page 17). Applicants respectfully traverse this rejection.

Applicants respectfully request that this rejection be held in abeyance until the remaining issues outstanding in this application have been resolved.

B. The '808 Application In View of Marasco, Rowlands and Zauderer

Claims 1-36, 38-44, 53-57, 59-65 and 69-79 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 46-128 of U.S. Patent Application No. 10/465,808 ("the '808 application"), in view of Marasco, Rowlands and Zauderer. (Office Action, page 26). Applicants respectfully traverse this rejection.

Applicants respectfully request that this rejection be held in abeyance until the remaining issues outstanding in this application have been resolved.

In addition, Applicants note that the '808 application was filed on June 20, 2003, while the present application (10/052,942) was filed on January 23, 2002. According to the MPEP § 804.I.A.1 (pg. 800-17):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Thus, if the nonstatutory obviousness-type double patenting rejection over the '808 application, in view of Marasco, Rowlands and Zauderer, is the only rejection remaining in the above-captioned application (*i.e.*, the "earlier filed of the two pending applications"), the double patenting rejection should be withdrawn without the need for a terminal disclaimer.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Tracy L. Muller
Attorney for Applicants
Registration No. 55,472

Date: February 15, 2007

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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